IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

REQUEST FOR FILING NATIONAL PHASE OF PCT APPLICATION UNDER 35 U.S.C. 371 AND 37 CFR 1.494 OR 1.495

To: Hon. Commissioner of Patents
Washington, D.C. 20231

00909

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

Atty Dkt: P 0284115 /Z.705541 PUS
M# /Client Ref.

From: Pillsbury Winthrop LLP, IP Group:

Date: December 4, 2001

This is a **REQUEST** for **FILING** a PCT/USA National Phase Application based on:

1. International Application	2. International Filing Date	3. Earliest Priority Date Claimed
PCT/GB00/02085	31 May 2000	4 June 1999
⇧ country code	Day MONTH Year	Day MONTH Year (use item 2 if no earlier priority)

4. Measured from the earliest priority date in item 3, this PCT/USA National Phase Application Request is being filed within:

(a) ☐ 20 months from above item 3 date (b) ☒ 30 months from above item 3 date,

(c) Therefore, the due date (unextendable) is December 4, 2001

5. Title of Invention INHIBITORS OF METALLOPROTEINASES

6. Inventor(s) TUCKER, Howard

Applicant herewith submits the following under 35 U.S.C. 371 to effect filing:

7. ☒ Please immediately start national examination procedures (35 U.S.C. 371 (f)).

8. ☒ **A copy of the International Application** as filed (35 U.S.C. 371(c)(2)) is transmitted herewith (file if in English but, if in foreign language, file only if not transmitted to PTO by the International Bureau) including:

a. ☒ Request;
b. ☒ Abstract;
c. 33 pgs. Spec. and Claims;
d. _____ sheet(s) Drawing which are ☐ informal ☐ formal of size ☐ A4 ☐ 11"

9. ☒ **A copy of the International Application has been transmitted by the International Bureau.**

10. **A translation of the International Application** into English (35 U.S.C. 371(c)(2))

a. ☐ is transmitted herewith including: (1) ☐ Request; (2) ☐ Abstract;
(3) _____ pgs. Spec. and Claims;
(4) _____ sheet(s) Drawing which are:
☐ informal ☐ formal of size ☐ A4 ☐ 11"

b. ☐ is not required, as the application was filed in English.

c. ☐ is not herewith, but will be filed when required by the forthcoming PTO Missing Requirements Notice per Rule 494(c) if box 4(a) is X'd or Rule 495(c) if box 4(b) is X'd.

d. ☐ Translation verification attached (not required now).

11. ☒ Please see the attached Preliminary Amendment

12. ☐ Amendments to the claims of the International Application **under PCT Article 19 (35 U.S.C. 371(c)(3)), i.e., before 18th month from first priority date above in item 3, are transmitted herewith (file only if in English) including:**

13. ☒ PCT Article 19 claim amendments (if any) have been transmitted by the International Bureau

14. ☐ Translation of the amendments to the claims **under PCT Article 19 (35 U.S.C. 371(c)(3)), i.e., of claim amendments** made before 18th month, **is attached (required by 20th month from the date in item 3 if box 4(a) above is X'd, or 30th month if box 4(b) is X'd, or else amendments will be considered canceled).**

15. **A declaration of the inventor** (35 U.S.C. 371(c)(4))
a. ☒ is submitted herewith ☒ Original ☐ Facsimile/Copy
b. ☐ is not herewith, but will be filed when required by the forthcoming PTO Missing Requirements Notice per Rule 494(c) if box 4(a) is X'd or Rule 495(c) if box 4(b) is X'd.

16. **An International Search Report (ISR):**
a. Was prepared by ☒ European Patent Office ☐ Japanese Patent Office ☐ Other
b. ☒ has been transmitted by the international Bureau to PTO.
c. ☒ copy herewith (2 pg(s).) ☒ plus Annex of family members (1 pg(s).).

17. **International Preliminary Examination Report** (IPER):
a. ☒ has been transmitted (if this letter is filed after 28 months from date in item 3) in English by the International Bureau with Annexes (if any) in original language.
b. ☒ copy herewith in English.
c.1 ☐ IPER Annex(es) in original language ("Annexes" are amendments made to claims/spec/drawings during Examination) including attached amended:
c.2 ☐ Specification/claim pages #_____ claims #_____
Dwg Sheets #_____
d. ☐ Translation of Annex(es) to IPER **(required by 30th month due date, or else annexed amendments will be considered canceled).**

18. **Information Disclosure Statement** including:
a. ☒ Attached Form PTO-1449 listing documents
b. ☐ Attached copies of documents listed on Form PTO-1449
c. ☒ A concise explanation of relevance of ISR references is given in the ISR.

19. ☒ **Assignment** document and Cover Sheet for recording are attached. Please mail the recorded assignment document back to the person whose signature, name and address appear at the end of this letter.

20. ☐ Copy of Power to IA agent.

21. ☐ **Drawings** (complete only if 8d or 10a(4) not completed): ___ sheet(s) per set: ☐ 1 set informal; ☐ Formal of size ☐ A4 ☐ 11"

22. Small Entity Status ☒ is **Not** claimed ☐ is claimed (**pre**-filing confirmation required)
22(a) _____ (No.) Small Entity Statement(s) enclosed (since 9/8/00 Small Entity Statements(s) not essential to make claim)

23. **Priority** is hereby claimed under 35 U.S.C. 119/365 based on the priority claim and the certified copy, both filed in the International Application during the international stage based on the filing in (country) EUROPE of:

	Application No.	Filing Date		Application No.	Filing Date
(1)	99401350.6	June 4, 1999	(2)		
(3)			(4)		
(5)			(6)		

a. ☒ See Form PCT/IB/304 sent to US/DO with copy of priority documents. If copy has not been received, please proceed promptly to obtain same from the IB.
b. ☐ Copy of Form PCT/IB/304 attached.

RE: USA National Phase Filing of PCT/GB00/02085

JC13 Rec'd PCT/PTO 04 DEC 2001

24. Attached: Copy of Form PCT/IB/306

25 Per Item 17.c2, **cancel original** pages #_____, claims #_____, Drawing Sheets #_____

26. **Calculation of the U.S. National Fee (35 U.S.C. 371 (c)(1)) and other fees is as follows:**
Based on amended claim(s) per above item(s) ☐ 12, ☐ 14, ☐ 17, ☐ 25 (hilite)

Total Effective Claims	13	minus 20 =	0	x $18/$9	=	$0	966/967
Independent Claims	6	minus 3 =	3	x $84/$42	=	$252	964/965
If any proper (ignore improper) Multiple Dependent claim is present,				add$280/$140		+280	968/969

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(4)): →→ **BASIC FEE REQUIRED, NOW** →→→→

A. If country code letters in item 1 are **not** "US","BR","BB","TT","MX","IL" "NZ", "IN" or "ZA"

See item 16 re:

1. Search Report was not prepared by EPO or JPO - - - - - - - - - add$1,040/$520 — 960/961
2. Search Report was prepared by EPO or JPO - - - - - - - - - - - - add$890/$445 +890 — 970/971

SKIP B, C, D AND E UNLESS country code letters in item 1 are "US","BR","BB","TT","MX","IL", "NZ", "IN" or "ZA"

☐ (X) →	☐	B.	If USPTO did not issue both International Search Report (ISR) and (if box 4(b) above is X'd) the International Examination Report (IPER), -	add$1,040/$520 0	+0 960/961
☐ (only) ☐ (one) →	☐	C.	If USPTO issued ISR but not IPER (or box 4(a) above is X'd), -	add$740/$370	+0 958/959
☐ (these) ☐ (4) → ☐ (boxes)	☐	D.	If USPTO issued IPER but IPER Sec. V boxes not all 3 YES, -	add$710/$355	+0 956/957
→	☐	E.	If international preliminary examination fee was paid to USPTO and Rules 492(a)(4) and 496(b) satisfied (IPER Sec. V all 3 boxes YES for all claims), - - - - - - - - - - - - -	add $100/$50	+0 962/963
☐ 27.				**SUBTOTAL =**	$1422

28. If Assignment box 19 above is X'd, add Assignment Recording fee of ----$40 +40 (581)

29. If box 15a is x'd, determine whether inventorship on Declaration is different than in international stage. If yes, add (per Rule 497(d) ----$130 + (098)

30. Attached is a check to cover the - **TOTAL FEES** $1462

Our Deposit Account No. 03-3975
Our Order No. 009901 (C#) | 0284115 (M#)

00909

CHARGE STATEMENT: The Commissioner is hereby authorized to charge any fee specifically authorized hereafter, or any missing or insufficient fee(s) filed, or asserted to be filed, or which should have been filed herewith or concerning any paper filed hereafter, and which may be required under Rules 16-18 and 492 (missing or insufficient fee only) now or hereafter relative to this application and the resulting Official document under Rule 20, or credit any overpayment, to our Account/Order Nos. shown above for which purpose a duplicate copy of this sheet is attached.
This CHARGE STATEMENT does not authorize charge of the issue fee until/unless an issue fee transmittal form is filed

Pillsbury Winthrop LLP
Intellectual Property Group

By Atty: Donald J. Bird **Reg. No.** 25323

Sig: _____ **Fax:** (703) 905-2500
Tel: (703) 905-2018

Atty/Sec: DJB/mhn

NOTE: File in duplicate with 2 postcard receipts (PAT-103) & attachments.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF

Inventor(s): TUCKER, Howard

Filed: Herewith

Title: INHIBITORS OF METALLOPROTEINASES

December 4, 2001

PRELIMINARY AMENDMENT

Hon. Commissioner of Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

IN THE SPECIFICATION:

At the top of the first page, just under the title, insert

☒ --This application is the National Phase of International Application PCT/GB00/02085 filed May 31, 2000 which designated the U.S. and that International Application

☒ was ☐ was not published under PCT Article 21(2) in English.--

Respectfully submitted,

PILLSBURY WINTHROP LLP
Intellectual Property Group

By: _____

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INHIBITORS OF METALLOPROTEINASES

The present invention relates to compounds useful in the inhibition of metalloproteinases and in particular to pharmaceutical compositions comprising these, as well as their use.

The compounds of this invention are inhibitors of one or more metalloproteinase enzymes. Metalloproteinases are a superfamily of proteinases (enzymes) whose numbers in recent years have increased dramatically. Based on structural and functional considerations these enzymes have been classified into families and subfamilies as described in N. M Hooper (1994) FEBS Letters 354:1-6. Examples of metalloproteinases include the matrix metalloproteinases (MMP) such as the collagenases (MMP1, MMP8, MMP13), the gelatinases (MMP2, MMP9), the stromelysins (MMP3, MMP10, MMP11), matrilysin (MMP7), metalloelastase (MMP12), enamelysin (MMP19), the MT-MMPs (MMP14, MMP15, MMP16, MMP17); the reprolysin or adamalysin or MDC family which includes the secretases and sheddases such as TNF converting enzymes (ADAM10 and TACE); the astacin family which include enzymes such as procollagen processing proteinase (PCP); and other metalloproteinases such as aggrecanase, the endothelin converting enzyme family and the angiotensin converting enzyme family.

Metalloproteinases are believed to be important in a plethora of physiological disease processes that involve tissue remodelling such as embryonic development, bone formation and uterine remodelling during menstruation. This is based on the ability of the metalloproteinases to cleave a broad range of matrix substrates such as collagen, proteoglycan and fibronectin. Metalloproteinases are also believed to be important in the processing, or secretion, of biological important cell mediators, such as tumour necrosis factor (TNF); and the post translational proteolysis processing, or shedding, of biologically important membrane proteins, such as the low affinity IgE receptor CD23 (for a more complete list see N. M. Hooper *et al.*, (1997) Biochem J. 321:265-279).

Metalloproteinases have been associated with many disease conditions. Inhibition of the activity of one or more metalloproteinases may well be of benefit in these disease conditions, for example: various inflammatory and allergic diseases such as, inflammation of the joint (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastro-intestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis), inflammation of the skin (especially psoriasis, eczema, dermatitis); in tumour metastasis or

invasion; in disease associated with uncontrolled degradation of the extracellular matrix such as osteoarthritis; in bone resorptive disease (such as osteoporosis and Paget's disease)); in diseases associated with aberrant angiogenesis; the enhanced collagen remodelling associated with diabetes, periodontal disease (such as gingivitis), corneal ulceration, ulceration of the skin, post-operative conditions (such as colonic anastomosis) and dermal wound healing; demyelinating diseases of the central and peripheral nervous systems (such as multiple sclerosis); Alzheimer's disease; and extracellular matrix remodelling observed in cardiovascular diseases such as restenosis and atheroscelerosis.

A number of metalloproteinase inhibitors are known; different classes of compounds may have different degrees of potency and selectivity for inhibiting various metalloproteinases. We have discovered a new class of compounds that are inhibitors of metalloproteinases and are of particular interest in inhibiting MMP-13. The compounds of this invention have beneficial potency and/or pharmacokinetic properties.

MMP13, or collagenase 3, was initially cloned from a cDNA library derived from a breast tumour [J. M. P. Freije *et al.* (1994) Journal of Biological Chemistry 269(24):16766-16773]. PCR-RNA analysis of RNAs from a wide range of tissues indicated that MMP13 expression was limited to breast carcinomas as it was not found in breast fibroadenomas, normal or resting mammary gland, placenta, liver, ovary, uterus, prostate or parotid gland or in breast cancer cell lines (T47-D, MCF-7 and ZR75-1). Subsequent to this observation MMP13 has been detected in transformed epidermal keratinocytes [N. Johansson *et al.*, (1997) Cell Growth Differ. 8(2):243-250], squamous cell carcinomas [N. Johansson *et al.*, (1997) Am. J. Pathol. *151(2)*:499-508] and epidermal tumours [K. Airola *et al.*, (1997) J. Invest. Dermatol. *109(2)*:225-231]. These results are suggestive that MMP13 is secreted by transformed epithelial cells and may be involved in the extracellular matrix degradation and cell-matrix interaction associated with metastasis especially as observed in invasive breast cancer lesions and in malignant epithelia growth in skin carcinogenesis.

Recent published data implies that MMP13 plays a role in the turnover of other connective tissues. For instance, consistent with MMP13's substrate specificity and preferential to degrade type II collagen [P. G. Mitchell *et al.*, (1996) J. Clin. Invest. *97(3)*:761-768; V. Knauper *et al.*, (1996) The Biochemical Journal 271:1544-1550], MMP13 has been hypothesised to serve a role during primary ossification and skeletal remodelling [M. Stahle-Backdahl *et al.*, (1997) Lab. Invest. 76(5):717-728; N. Johansson *et al.*, (1997) Dev. Dyn. 208(3):387-397], in destructive joint diseases such as rheumatoid and osteo-arthritis [D.

Wernicke *et al.*, (1996) J. Rheumatol. 23:590-595; P. G. Mitchell et al., (1996) J. Clin. Invest. 97(3):761-768; O. Lindy *et al.*, (1997) Arthritis Rheum 40(8):1391-1399]; and during the aseptic loosening of hip replacements [S. Imai *et al.*, (1998) J. Bone Joint Surg. Br. 80(4):701-710]. MMP13 has also been implicated in chronic adult periodontitis as it has been localised to the epithelium of chronically inflamed mucosa human gingival tissue [V. J. Uitto *et al.*, (1998) Am. J. Pathol 152(6):1489-1499] and in remodelling of the collagenous matrix in chronic wounds [M. Vaalamo *et al.*, (1997) J. Invest. Dermatol. 109(1):96-101].

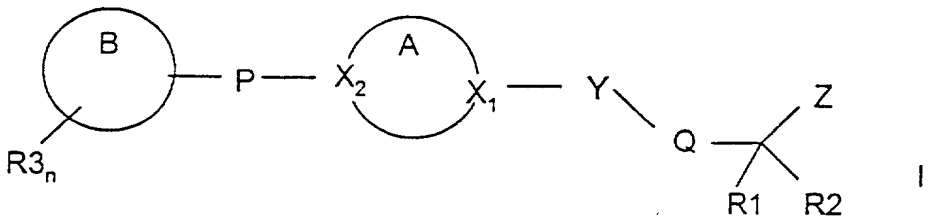
MMP9 (Gelatinase B; 92kDa TypeIV Collagenase; 92kDa Gelatinase) is a secreted protein which was first purifed, then cloned and sequenced, in 1989 (S.M. Wilhelm et al (1989) J. Biol Chem. 264 (29) : 17213-17221. Published erratum in J. Biol Chem. (1990) 265 (36) : 22570.). A recent review of MMP9 provides an excellent source for detailed information and references on this protease : T.H. Vu & Z. Werb (1998) (In : Matrix Metalloproteinases. 1998. Edited by W.C. Parks & R.P. Mecham. pp115 - 148. Academic Press. ISBN 0-12-545090-7). The following points are drawn from that review by T.H. Vu & Z. Werb (1998).

The expression of MMP9 is restricted normally to a few cell types, including trophoblasts, osteoclasts, neutrophils and macrophages. However, its expression can be induced in these same cells and in other cell types by several mediators, including exposure of the cells to growth factors or cytokines. These are the same mediators often implicated in initiating an inflammatory response. As with other secreted MMPs, MMP9 is released as an inactive pro-enzyme which is subsequently cleaved to form the enzymatically active enzyme. The proteases required for this activation *in vivo* are not known. The balance of active MMP9 versus inactive enzyme is further regulated *in vivo* by interaction with TIMP-1 (Tissue Inhibitor of Metalloproteinases -1), a naturally-occurring protein. TIMP-1 binds to the C-terminal region of MMP9, leading to inhibition of the catalytic domain of MMP9. The balance of induced expression of ProMMP9, cleavage of Pro- to active MMP9 and the presence of TIMP-1 combine to determine the amount of catalytically active MMP9 which is present at a local site. Proteolytically active MMP9 attacks substrates which include gelatin, elastin, and native Type IV and Type V collagens; it has no activity against native Type I collagen, proteoglycans or laminins.

There has been a growing body of data implicating roles for MMP9 in various physiological and pathological processes. Physiological roles include the invasion of embryonic trophoblasts through the uterine epithelium in the early stages of embryonic

implantation; some role in the growth and development of bones; and migration of inflammatory cells from the vasculature into tissues. Increased MMP9 expression has been observed in certain pathological conditions, thereby implicating MMP9 in disease processes such as arthritis, tumour metastasis, Alzheimer's, Multiple Sclerosis, and plaque rupture in atherosclerosis leading to acute coronary conditions such as Myocardial Infarction.

In a first aspect of the invention we provide compounds of the formula I



I

wherein ring B is a monocyclic or bicyclic alkyl, aryl, aralkyl, heteroaryl or heteroaralkyl ring comprising up to 12 ring atoms and containing one or more heteroatoms independently chosen from N, O, and S; alternatively ring B may be biphenyl; ring B may optionally be linked to ring A by a C1-4 alkyl or a C1-4 alkoxy chain linking the 2-position of ring B with a carbon atom alpha to X2;

each R3 is independently selected from hydrogen, halogen, NO2, COOR wherein R is hydrogen or C1-6alkyl, CN, CF3, C1-6 alkyl, -S-C1-6 alkyl, -SO-C1-6 alkyl, -SO2-C1-6 alkyl ,C1-6 alkoxy and up to C10 aryloxy, n is 1,2 or 3;

P is $-(CH_2)n-$ wherein n = 0, 1, 2, or P is an alkene or alkyne chain of up to six carbon atoms; where X2 is C, P may be -Het-, -(CH[R6])n-Het-, -Het-(CH[R6]n-or -Het-(CH[R6])n-Het-, wherein Het is selected from - CO-, -S-, SO-, -SO2-, -NR6- , or -O- wherein n is 1 or 2, or P may be selected from -CO-N(R6)-, -N(R6)-CO-, -SO2-N(R6)- and -N(R6)-SO2-, and R6 is hydrogen, C1-6 alkyl, up to C10 aralkyl or up to C9 heteroalkyl;

Ring A is a 5-7 membered aliphatic ring and may optionally be mono- or di-substituted by optionally substituted C1-6 alkyl or C1-6 alkoxy, each substituent being independently selected from halogen, C1-6 alkyl or an oxo group;

X1 and X2 are independently selected from N and C, where a ring substituent on ring A is an oxo group this is preferably adjacent a ring nitrogen atom;

Y is selected from -SO2- and -CO-;

Z is -CONHOH , Y is -CO- and Q is selected from -C(R6)(R7)-, -C(R6)(R7)-CH2-, -N(R6)-, and -N(R6)-CH2- wherein R6 is as defined above, and solely in relation to Q as here defined, R6 may also represent up to C10 aryl and up to C9 heteroaryl, and R7 is H, C1-6 alkyl, or together with R6 forms a carbocyclic or heterocyclic spiro 5, 6 or 7 membered ring, the latter containing at least one heteroatom selected from N, O, and S;

Z is -CONHOH, Y is -SO2- and Q is selected from -C(R6)(R7)-, and —C(R6)(R7)-CH2-;

or Z is -N(OH)CHO and Q is selected from -CH(R6)-,-CH(R6)-CH2-, and -N(R6)-CH2-;

R1 is H, or C1-6 alkyl;

Z is selected from -COOH, -CONHOH, -N(OH)CHO and N(OH)COR wherein R is C1-6alkyl, up to C10 aryl and up to C9 aralkyl

and R2 is a heterocyclylalkyl ring having 5-7 ring atoms and comprising one or two ring heteroatoms independently selected from oxygen, nitrogen and sulphur, the ring being optionally substituted by (i) Y-R9 wherein R9 is C1-6 alkyl, up to C10 aryl, up to C12 aralkyl or up to C12 heteroaryl(hetero)alkyl, or (ii) Y-T-R9 wherein Y and R9 are as previously defined and T is oxygen or N-R8 wherein R8 is hydrogen or C1-6alkyl, the heteroatom(s) being independently selected from oxygen, nitrogen and sulphur; R9 and R8 independently being optionally substituted by one or two groups selected from halogen, NO2, CN, CF3, C1-6 alkyl, -S-C1-6 alkyl, -SO-C1-6 alkyl, -SO2-C1-6 alkyl and C1-6 alkoxy.

Any alkyl groups outlined above may be straight chain or branched.

Convenient values for the above groups include the following:

ring A = a 5-6 membered aliphatic ring, such as a piperazine or piperidine ring, and may optionally be mono- or di-substituted by optionally substituted C1-6 alkyl or C1-6 alkoxy, each substituent being independently selected from halogen, C1-6 alkyl or an oxo group;

R3 = hydrogen, halogen, NO2, CF3, C1-4 alkyl, and C1-4 alkoxy, n is 1 or 2, such as individually 4-fluoro, CF3, 4-chloro and 3,4-dichloro;.

ring B = monocyclic or bicyclic cycloalkyl, aryl, aralkyl or heteroaryl having up to 10 ring atoms, especially monocyclic aryl, aralkyl or heteroaryl having up to 7 ring atoms, more especially monocyclic aryl or heteroaryl having up to 6 ring atoms, such as a phenyl or pyridyl ring;

P = -(CH2)n- wherein n is 0 or 1, or P is -NH-CO-

one or both of X2 and X1 = N

Y = -SO2- or -CO-;

Q = -CH(R6)-, -CH(R6)-CH2-, -N(R6)-, and -N(R6)-CH2- wherein R6 is hydrogen or C1-6 alkyl; when Q = -N(R6)-, or -N(R6)-CH2- then Y may also be -CS-; especially Q= -CH(R6)- wherein R6 is hydrogen or C1-4 alkyl such as propyl or butyl, particularly propyl.; also where Q is linked to R1 or R2 to form a 5-7 alkyl or heteroalkyl ring such as a cyclohexyl ring;

R1 = hydrogen, or C1-4 alkyl.

Z = -CONHOH- or -N(OH)CHO

and R2 is a heterocyclylalkyl ring having 5-7 ring atoms and comprising one or two ring heteroatoms independently selected from oxygen, nitrogen and sulphur, the ring being optionally substituted by (i) Y-R9 wherein R9 is C1-6 alkyl, up to C10 aryl, up to C12 aralkyl or up to C12 heteroaryl(hetero)alkyl, or (ii) Y-T-R9 wherein Y and R9 are as previously defined and T is oxygen or N-R8 wherein R8 is hydrogen or C1-6alkyl, the heteroatom(s) being independently selected from oxygen, nitrogen and sulphur; R9 and R8 independently being optionally substituted by one or two groups selected from halogen, NO2, CN, CF3, C1-6 alkyl, -S-C1-6 alkyl, -SO-C1-6 alkyl, -SO2-C1-6 alkyl and C1-6 alkoxy.

Preferred values for the above groups include the following:

R3 = hydrogen, chlorine, fluorine, NO2, CF3, methyl, ethyl, methoxy, ethoxy, particularly methoxy or fluorine;

ring B = phenyl, biphenyl, napthyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl, especially phenyl or pyridyl, more especially phenyl or 2-pyridyl;

ring A = piperazine;

P = a direct bond;

both X2 and X1 are N;

Y = -SO2-;

Q = -CH2-;

R2 is a heterocyclylalkyl ring having 5-7 ring atoms and comprising one or two ring heteroatoms independently selected from oxygen, nitrogen and sulphur, the ring being optionally substituted by (i) Y-R9 wherein Y is -SO2- or -CO- and R9 is C1-6 alkyl or alkylamino, up to C10 aryl or arylamino, up to C12 aralkyl or aralkylamino or up to C12 heteroaryl(hetero)alkyl, R9 independently being optionally substituted by one or two groups

selected from halogen, NO2, CN, CF3, C1-6 alkyl, -S-C1-6 alkyl, -SO-C1-6 alkyl, -SO2-C1-6 alkyl and C1-6 alkoxy;

R1 is hydrogen;

Z is -N(OH)CHO;

More preferred values include:

R3 being methoxy, fluorine or 4-fluoro;

ring A is unsubstituted;

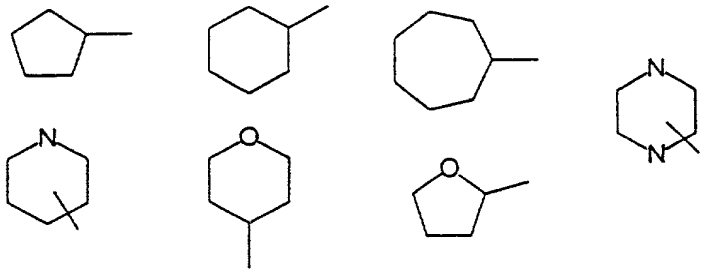
ring B is phenyl, pyridyl, or 2-pyridyl;

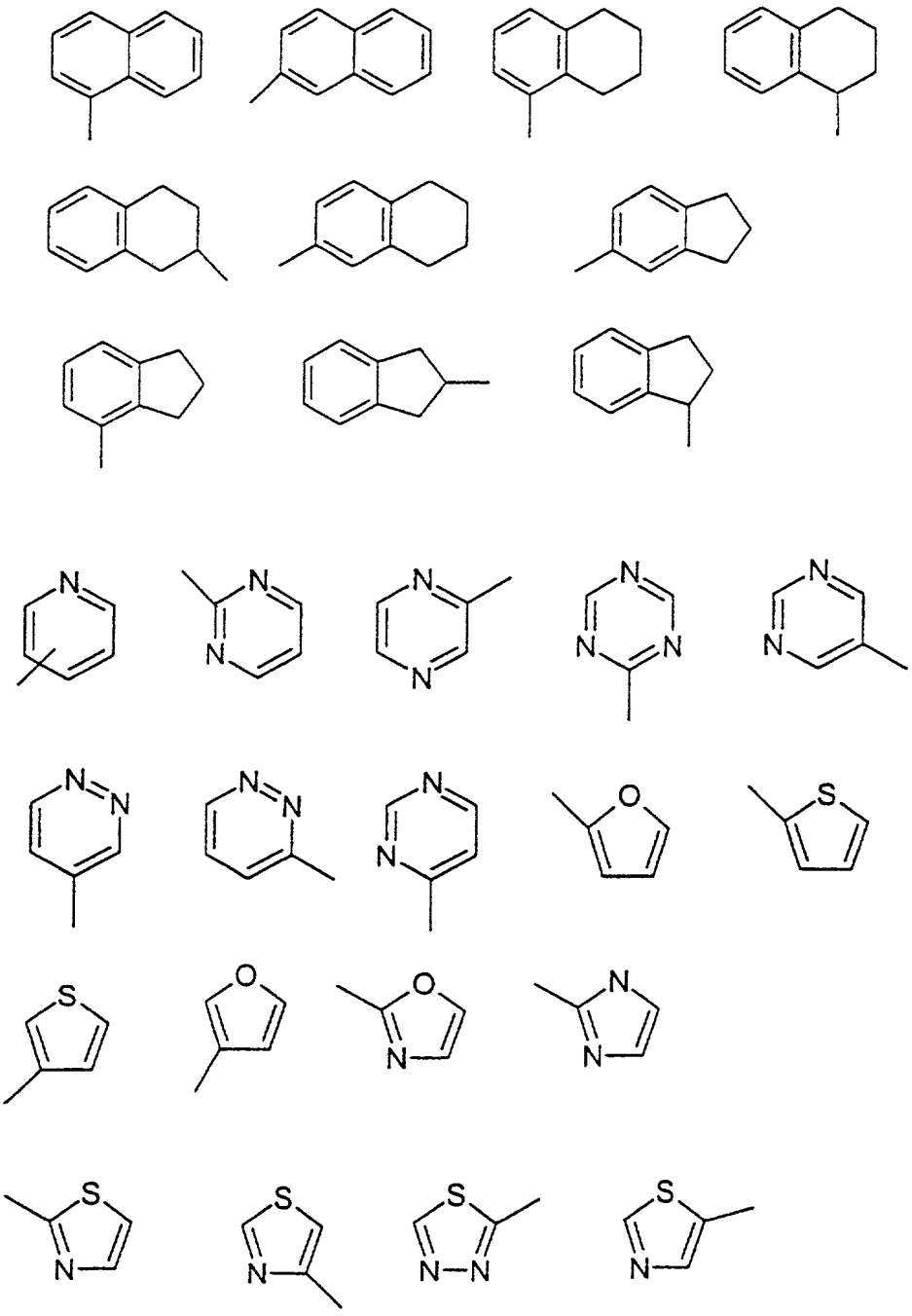
R2 is 3- or 4-piperidinyl, optionally N-substituted by Y-R9 wherein Y is -SO2- or -CO- and R9 is C1-4 alkyl or alkylamino, C6 aryl or arylamino, up to C10 aralkyl or aralkylamino or up to C10 heteroaryl(hetero)alkyl, R9 independently being optionally substituted by one or two groups selected from halogen, CF3, and C1-4 alkyl;

Preferred combinations of Rings A and B include phenyl and piperazinyl; pyridyl and piperazinyl respectively.

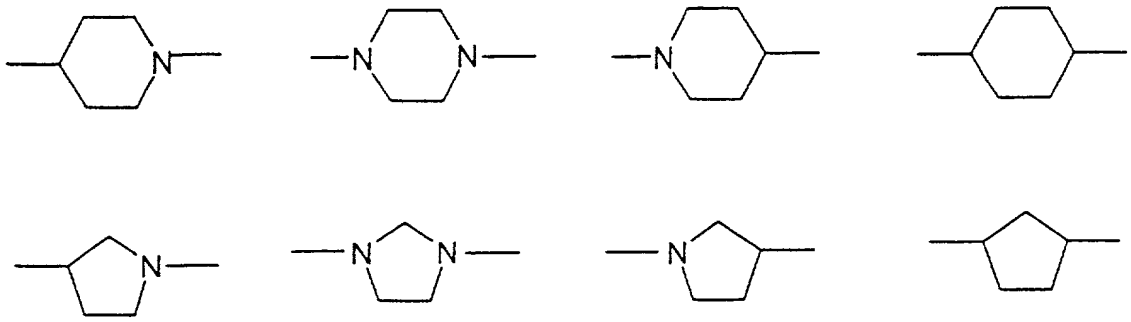
Particular compounds include those where Ring A is unsubstituted.

Particular alicyclic, fused and heterocyclic rings for ring B include any one of





Particular rings for ring A include any one of



and its corresponding seven membered analogue(s).

It will be appreciated that the particular substitituents and number of substituents on rings A and B are selected so as to avoid sterically undesirable combinations.

Where optically active centres exist in the compounds of formula I, we disclose all individual optically active forms and combinations of these as individual specific embodiments of the invention, as well as their corresponding racemates.

The above compounds are potent MMP13 inhbitors, they also have good aggrecanase activity. As previously outlined the compounds of the invention are metalloproteinase inhibitors, in particular they are inhibitors of MMP13. Each of the above indications for the compounds of the formula I represents an independent and particular embodiment of the invention. Whilst we do not wish to be bound by theoretical considerations, the compounds of the invention are believed to show selective inhibition for any one of the above indications relative to any MMP1 inhibitory activity, by way of non-limiting example they may show 100-1000 fold selectivity over any MMP1 inhibitory activity.

The compounds of the invention may be provided as pharmaceutically acceptable salts. These include acid addition salts such as hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine.

They may also be provided as in vivo hydrolysable esters. These are pharmaceutically acceptable esters that hydrolyse in the human body to produce the parent compound. Such esters can be identified by administering, for example intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluids. Suitable in vivo hydrolysable esters for carboxy include methoxymethyl and for hydroxy include acetyl.

In order to use a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically acceptable salt or an in vivo hydrolysable ester and pharmaceutically acceptable carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal adminstration or by inhalation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more disease conditions referred to hereinabove.

The pharmaceutical compositions of this invention will normally be administered to humans so that, for example, a daily dose of 0.5 to 75 mg/kg body weight (and preferably of 0.5 to 30 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

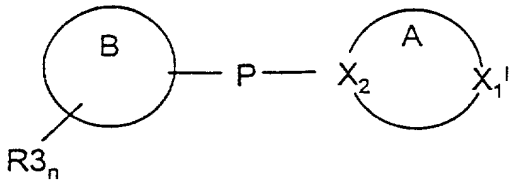
Therefore in a further aspect, the present invention provides a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof for use in a method of therapeutic treatment of the human or animal body.

In yet a further aspect the present invention provides a method of treating a metalloproteinase mediated disease condition which comprises administering to a warm-

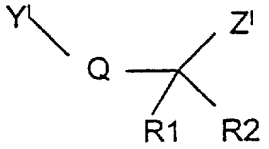
blooded animal a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof.

In another aspect the present invention provides a process for preparing a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof which process comprises

a) reacting a compound of the formula (II) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof with a compound of the formula (III)



II



III

wherein X_1^I represents X or a precursor of X (whether by modification or displacement) or an activated form of X suitable for reaction with Y_1;

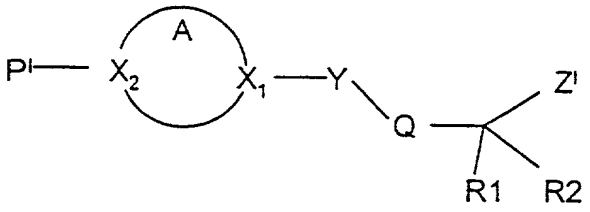
Y_1 represents Y, a precursor of Y, or an activated form of Y suitable for reaction with X_1^I;

by way of non-limiting example, when X is C then X_1 may be derivatised to include a precursor of Y for reaction with a compound of formula III wherein Y^I is a precursor of Y;

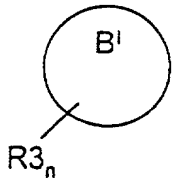
Z^I represents a protected form of Z, a precursor of Z (whether by modification or displacement of Z^I) or an activated form of Z;

or

b) reacting a compound of the formual (IV)) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof with a compound of the formula (V).



IV



V

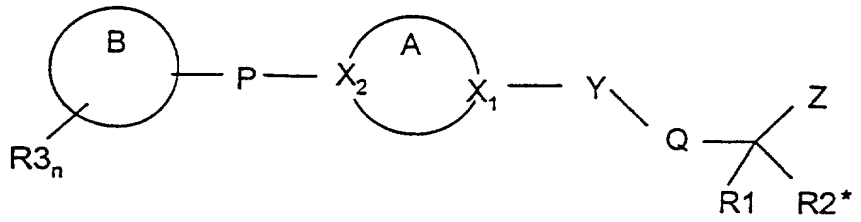
wherein B^I represents a suitable ring function or substituent group for reaction with P^i;

Z^I is as hereinbefore defined; and

P^i represents a suitably activated form of the linker P for reaction with B^I;

or

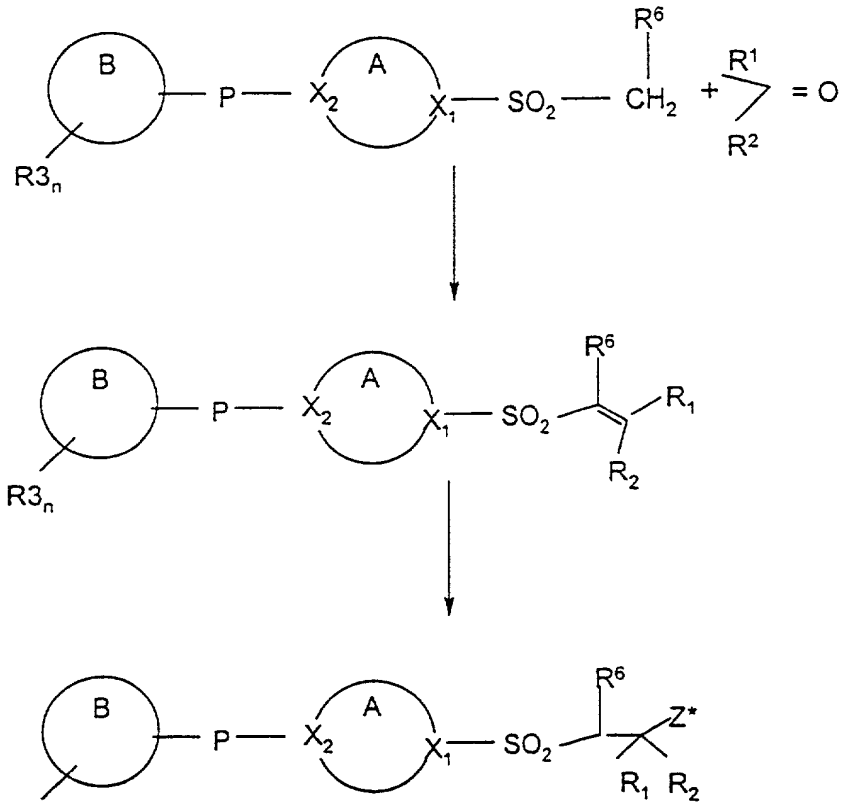
c) reacting a compound of the general formula (VIII)



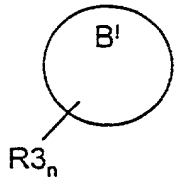
wherein R2* is a precursor for R2 with appropriate reagent(s) in one or more steps to yield R2. The group Z is conveniently protected during such steps. By way of non-limiting example R2* is a piperidine or piperazine ring;

or

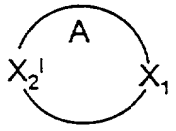
(d) reacting a compound of the formula IX with an appropriate compound of the formula R1-CO-R2 to yield an alkene of the formula X, which is then converted to a compound of the formula XI wherein Z* is a hydroxylamine precursor of the group Z, and then converting Z* to the group Z, all as set out below:



A compound of the formula (II) is conveniently prepared by reacting a compound of the formual (VI) with a compound of the formula (VII)



VI

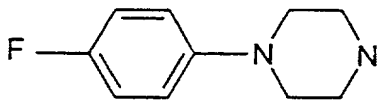


VII

wherein B^I represents a suitable ring function or substituent group, X_2^I represents X or a precursor of X (whether by modification or displacement) or an activated form of X suitable for reaction with B^I and wherein B^I and X_2^I when reacted together provide the linker P

between ring B and ring A in the compound of formula (II). By way of non-limiting example, when $X_2$is N then ring A is suitably derivatised to introduce the linker P via B^1, and when X_2 is C then both ring A and ring are suitably derivatised to provide the linker P by the reaction of B^1 and X_2^1.

Convenient commercially available starting materials include



The compounds of the invention may be evaluated for example in any one of the following assays:

Isolated Enzyme Assays:

Matrix Metalloproteinase family, including for example MMP13

Recombinant human proMMP13 may be expressed and purified as described by Knauper *et al.* [V. Knauper *et al.*, (1996) The Biochemical Journal 271:1544-1550 (1996)]. The purified enzyme can be used to monitor inhibitors of activity as follows: purified proMMP13 is activated using 1mM amino phenyl mercuric acid (APMA), 20 hours at 21°C; the activated MMP13 (11.25ng per assay) is incubated for 4-5 hours at 35°C in assay buffer (0.1M Tris-HCl, pH 7.5 containing 0.1M NaCl, 20mM $CaCl_2$, 0.02 mM ZnCl and 0.05% (w/v) Brij 35 using the synthetic substrate 7-methoxycoumarin-4-yl)acetyl.Pro.Leu.Gly.Leu.N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl.Ala.Arg.NH_2 in the presence or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 328nm and λem 393nm. Percent inhibition is calculated as follows: % Inhibition is equal to the [$Fluorescence_{plus\ inhibitor}$ - $Fluorescence_{background}$] divided by the [$Fluorescence_{minus\ inhibitor}$ - $Fluorescence_{background}$].

A similar protocol can be used for other expressed and purified pro MMPs using substrates and buffers conditions optimal for the particular MMP, for instance as described in C. Graham Knight *et al.*, (1992) FEBS Lett. 296(3):263-266.

Adamalysin family, including for example TNF convertase.

The ability of the compounds to inhibit proTNFα convertase enzyme may be assessed using a partially purified, isolated enzyme assay, the enzyme being obtained from the

membranes of THP-1 as described by K. M. Mohler *et al.*, (1994) Nature 370:218-220. The purified enzyme activity and inhibition thereof is determined by incubating the partially purified enzyme in the presence or absence of test compounds using the substrate 4',5'-Dimethoxy-fluoresceinyl Ser.Pro.Leu.Ala.Gln.Ala.Val.Arg.Ser.Ser.Ser.Arg.Cys(4-(3-succinimid-1-yl)-fluorescein)-NH_2 in assay buffer (50mM Tris HCl, pH 7.4 containing 0.1% (w/v) Triton X-100 and 2mM $CaCl_2$), at 26°C for 18 hours. The amount of inhibition is determined as for MMP13 except λex 490nm and λem 530nm were used. The substrate was synthesised as follows. The peptidic part of the substrate was assembled on Fmoc-NH-Rink-MBHA-polystyrene resin either manually or on an automated peptide synthesiser by standard methods involving the use of Fmoc-amino acids and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) as coupling agent with at least a 4- or 5-fold excess of Fmoc-amino acid and HBTU. Ser^1 and Pro^2 were double-coupled. The following side chain protection strategy was employed; $Ser^1(Bu^t)$, Gln^5(Trityl), $Arg^{8,12}$(Pmc or Pbf), $Ser^{9,10,11}$(Trityl), Cys^{13}(Trityl). Following assembly, the N-terminal Fmoc-protecting group was removed by treating the Fmoc-peptidyl-resin with in DMF. The amino-peptidyl-resin so obtained was acylated by treatment for 1.5-2hr at 70°C with 1.5-2 equivalents of 4',5'-dimethoxy-fluorescein-4(5)-carboxylic acid [Khanna & Ullman, (1980) Anal Biochem. 108:156-161) which had been preactivated with diisopropylcarbodiimide and 1-hydroxybenzotriazole in DMF]. The dimethoxyfluoresceinyl-peptide was then simultaneously deprotected and cleaved from the resin by treatment with trifluoroacetic acid containing 5% each of water and triethylsilane. The dimethoxyfluoresceinyl-peptide was isolated by evaporation, trituration with diethyl ether and filtration. The isolated peptide was reacted with 4-(N-maleimido)-fluorescein in DMF containing diisopropylethylamine, the product purified by RP-HPLC and finally isolated by freeze-drying from aqueous acetic acid. The product was characterised by MALDI-TOF MS and amino acid analysis.

Natural Substrates

The activity of the compounds of the invention as inhibitors of aggrecan degradation may be assayed using methods for example based on the disclosure of E. C. Arner *et al.*, (1998) Osteoarthritis and Cartilage 6:214-228 and the antibodies described therein. The potency of compounds to act as inhibitors against collagenases can be determined as described by T. Cawston and A. Barrett (1979) Anal. Biochem. 99:340-345.

Inhibition of Metalloproteinase Activity in Cell/Tissue Based Activity:

Test as an agent to inhibit membrane sheddases such as TNF convertase

The ability of the compounds of this invention to inhibit the cellular processing of TNFα production may be assessed in THP-1 cells using an ELISA to detect released TNF essentially as described K. M. Mohler *et al.*, (1994) Nature 370:218-220. In a similar fashion the processing or shedding of other membrane molecules such as those described in N. M. Hooper *et al.*, (1997) Biochem. J. 321:265-279 may be tested using appropriate cell lines and with suitable antibodies to detect the shed protein.

Test as an agent to inhibit cell based invasion

The ability of the compound of this invention to inhibit the migration of cells in an invasion assay may be determined as described in A. Albini *et al.*, (1987) Cancer Research 47:3239-3245.

Test as an agent to inhibit whole blood TNF sheddase activity

The ability of the compounds of this invention to inhibit TNFα production is assessed in a human whole blood assay where LPS is used to stimulate the release of TNFα. Heparinized (10Units/ml) human blood obtained from volunteers is diluted 1:5 with medium (RPMI1640 + bicarbonate, penicillin, streptomycin and glutamine) and incubated (160μl) with 20μl of test compound (triplicates), in DMSO or appropriate vehicle, for 30 min at 37°C in a humidified (5%CO_2/95%air) incubator, prior to addition of 20μl LPS (E. coli. 0111:B4; final concentration 10μg/ml). Each assay includes controls of diluted blood incubated with medium alone (6 wells/plate) or a known TNFα inhibitor as standard. The plates are then incubated for 6 hours at 37°C (humidified incubator), centrifuged (2000rpm for 10 min; 4°C), plasma harvested (50-100μl) and stored in 96 well plates at -70°C before subsequent analysis for TNFα concentration by ELISA.

Test as an agent to inhibit in vitro cartilage degradation

The ability of the compounds of this invention to inhibit the degradation of the aggrecan or collagen components of cartilage can be assessed essentially as described by K. M. Bottomley *et al.*, (1997) Biochem J. 323:483-488.

Pharmacodynamic test

To evaluate the clearance properties and bioavailability of the compounds of this invention an ex vivo pharmacodynamic test is employed which utilises the synthetic substrate assays above or alternatively HPLC or Mass spectrometric analysis. This is a generic test

which can be used to estimate the clearance rate of compounds across a range of species. Animals (e.g. rats, marmosets) are dosed iv or po with a soluble formulation of compound (such as 20%w/v DMSO, 60% w/v PEG400) and at subsequent time points (e.g. 5, 15, 30, 60, 120, 240, 480, 720, 1220 mins) the blood samples are taken from an appropriate vessel into 10U heparin. Plasma fractions are obtained following centrifugation and the plasma proteins precipitated with acetonitrile (80%w/v final concentration). After 30 mins at -20°C the plasma proteins are sedimented by centrifugation and the supernatant fraction is evaporated to dryness using a Savant speed vac. The sediment is reconstituted in assay buffer and subsequently analysed for compound content using the synthetic substrate assay. Briefly, a compound concentration-response curve is constructed for the compound undergoing evaluation. Serial dilutions of the reconstituted plasma extracts are assessed for activity and the amount of compound present in the original plasma sample is calculated using the concentration-response curve taking into account the total plasma dilution factor.

In Vivo Assessment

Test as an anti-TNF agent

The ability of the compounds of this invention as *ex vivo* TNFα inhibitors is assessed in the rat. Briefly, groups of male [Wistar Alderley Park (AP)] rats (180-210g) are dosed with compound (6 rats) or drug vehicle (10 rats) by the appropriate route e.g. peroral (p.o.), intraperitoneal (i.p.) , subcutaneous (s.c.). Ninety minutes later rats are sacrificed using a rising concentration of CO_2 and bled out via the posterior vena cavae into 5 Units of sodium heparin/ml blood. Blood samples are immediately placed on ice and centrifuged at 2000 rpm for 10 min at 4°C and the harvested plasmas frozen at -20°C for subsequent assay of their effect on TNFα production by LPS-stimulated human blood. The rat plasma samples are thawed and 175µl of each sample are added to a set format pattern in a 96U well plate. Fifty µl of heparinized human blood is then added to each well, mixed and the plate is incubated for 30 min at 37°C (humidified incubator). LPS (25µl; final concentration10µg/ml) is added to the wells and incubation continued for a further 5.5 hours. Control wells are incubated with 25µl of medium alone. Plates are then centrifuged for 10 min at 2000 rpm and 200µl of the supernatants are transferred to a 96 well plate and frozen at -20°C for subsequent analysis of TNF concentration by ELISA.

Data analysis by dedicated software calculates for each compound/dose:

Percent inhibition of TNFα= $\frac{\text{Mean TNFα (Controls) - Mean TNFα (Treated) X 100}}{\text{Mean TNFα (Controls)}}$

Test as an anti-arthritic agent

Activity of a compound as an anti-arthritic is tested in the collagen-induced arthritis (CIA) as defined by D. E. Trentham *et al.*, (1977) J. Exp. Med. 146,:857. In this model acid soluble native type II collagen causes polyarthritis in rats when administered in Freunds incomplete adjuvant. Similar conditions can be used to induce arthritis in mice and primates.

Test as an anti-cancer agent

Activity of a compound as an anti-cancer agent may be assessed essentially as described in I. J. Fidler (1978) Methods in Cancer Research 15:399-439, using for example the B16 cell line (described in B. Hibner *et al.*, Abstract 283 p75 10th NCI-EORTC Symposium, Amsterdam June 16 - 19 1998).

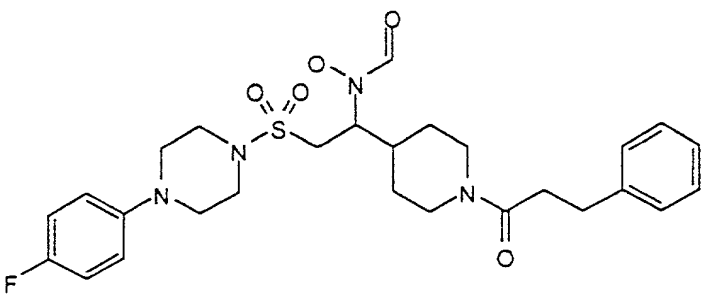
The invention will now be illustrated but not limited by the following Examples:

EXAMPLES

Example 1

Acetic anhydride (1 ml) was added dropwise to formic acid (3 ml) at 0°C and the mixture was stirred at 0°C for 30 minutes. This mixture was added dropwise to a solution of 4-(4-fluorophenyl)-1-[2-(1-phenethylcarbonylpiperidin-4-yl)-2-hydroxylaminoethylsuphonyl]-piperazine (0.65 g) in tetrahydrofuran (5 ml) at 0°C and the mixture was allowed to warm to ambient temperature and was stirred for 10 hours. The reaction mixture was evaporated to small volume, aqueous sodium bicarbonate was added and the mixture was extracted with ethyl acetate (2x25 ml).

The ethyl acetate extracts were dried and evaporated to dryness. The gum so obtained was subjected to chromatography on silica eluted initially with an ethyl acetate:isohexane mixture (3:2 v/v) and then an ethyl acetate;methanol mixture (9:1). There was obtained **4-(4-fluorophenyl)-1-[2-(1-phenethylcarbonylpiperidin-4-yl)-2-{O-formylhydroxylamino}ethylsuphonyl]-piperazine** as a gum, yield 230 mg, M+H = 547.

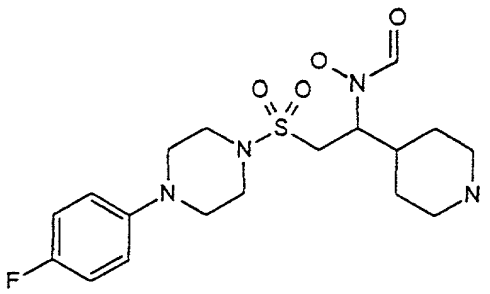


A mixture of 4-(4-fluorophenyl)-1-[2-(1-phenethylcarbonylpiperidin-4-yl)-ethenylsulphonyl]-piperazine (0.75 g) and 50% aqueous hydroxylamine (5 ml) in tetrahydrofuran (10 ml) was stirred for 48 hours. The mixture was evaporated to dryness and water (20 ml) was added. The mixture was extracted with ethyl acetate (2 x 15 ml) and the extracts were washed with water and dried. Removal of the solvent gave 4-(4-fluorophenyl)-1-[2-(1-phenethylcarbonylpiperidin-4-yl)-2-hydroxylaminoethylsuphonyl]-piperazine (0.65 g) as a gum, M+H = 519 (518).

3-Phenylpropionyl chloride (0.21 ml) was added dropwise to a solution of 4-(4-fluorophenyl)-1-[2-(piperidin-4-yl)-ethenylsulphonyl]-piperazine (0.5 g) in dichloromethane containing triethylamine (0.2 ml). The mixture was stirred for 3hours, evaporated to dryness, diluted with water and extracted with ethyl acetate (2 x 15 ml). The ethyl acetate extracts were combined and washed with aqueous sodium bicarbonate, water and dried. Removal of the solvent gave 4-(4-fluorophenyl)-1-[2-(1-phenethylcarbonylpiperidin-4-yl)-ethenylsulphonyl]-piperazine as a gum, M+H = 486 (485).

A mixture of 4-(4-fluorophenyl)-1-[2-(1-t-butoxycarbonylpiperidin-4-yl)-ethenylsulphonyl]-piperazine (1.96 g) and trifluoroacetic acid (5 ml) was stirred at ambient temperature for 5 hours. The mixture was evaporated to dryness, diluted with water, basified with aqueous 2M sodium hydroxide and extracted with ethyl acetate (2 x 20 ml). Removal of the solvent gave 4-(4-fluorophenyl)-1-[2-(piperidin-4-yl)-ethenylsulphonyl]-piperazine.

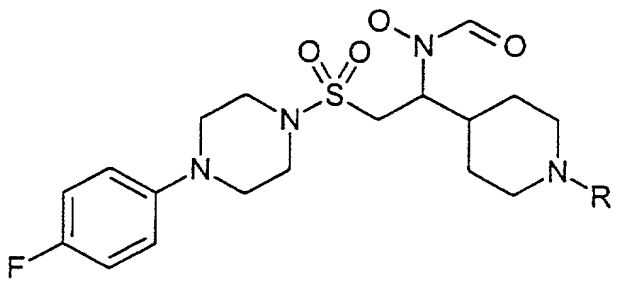
In like manner using 4-(4-fluorophenyl)-1-[2-(1-t-butoxycarbonylpiperidin-4-yl)-2-{O-formylhydroxylamino}ethylsuphonyl]-piperazine as starting material there was obtained 4-(4-fluorophenyl)-1-[2-(piperidin-4-yl)]-2-{O-formylhydroxylamino}ethylsuphonyl]-piperazine, M+H = 415.

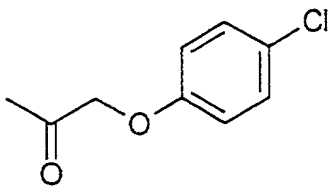


n-Butyl lithium (8.6 ml of a 1.6 M solution in THF) was added dropwise to a suspension of 4-(4-fluorophenyl)-1-methanesulphonylpiperazine (3.52 g) in THF (40 ml) at -78 °C and the mixture was stirred for 30 minutes. Diethylchlorophosphate (1.97 ml) was added dropwise and the mixture was stirred at -78 °C for a further 30 minutes. n-Butyl lithium (8.6 ml of a 1.6 M solution in THF) was added dropwise and stirred for 30 minutes. A solution of 1-(t-butoxycarbonyl)-piperidine-4-aldehyde (2.91 g) in THF (5 ml) was added dropwise and the mixture was allowed to warm to ambient temperature and was stired for 10 hours. Saturated aqueous ammonium chloride solution (5 ml) was added, the reaction mixture was diluted with ethyl acetate (25 ml) and washed with water. Removal of the solvent gave 4-(4-fluorophenyl)-1-[2-(1-t-butoxycarbonylpiperidin-4-yl)-ethenylsulphonyl]-piperazine as a gum which solidified on standing, M+H = 455 (454).

Example 2

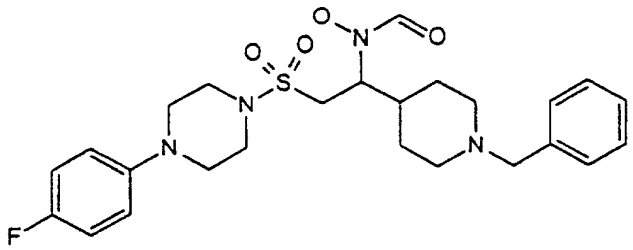
In like manner there were prepared compounds of the formula:

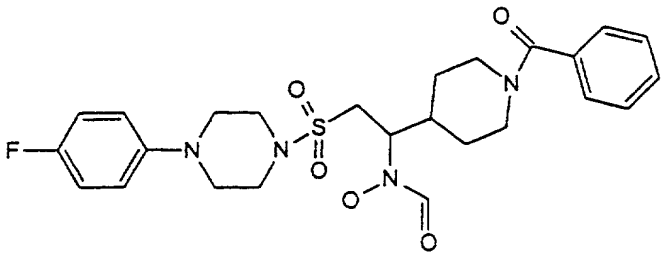


R	M+H
-COOBu^t	515
	583

Example 3

Using procedures analogous to those outlined in Example 1 there were prepared:





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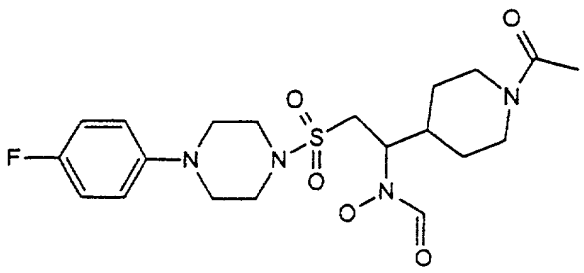

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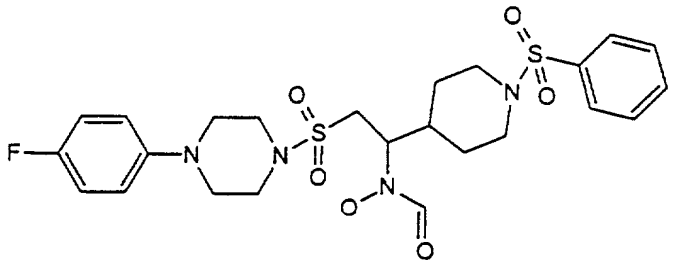

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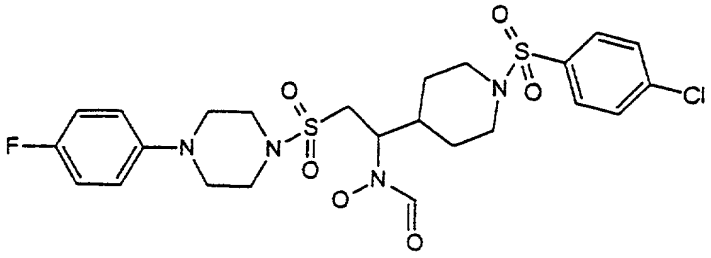

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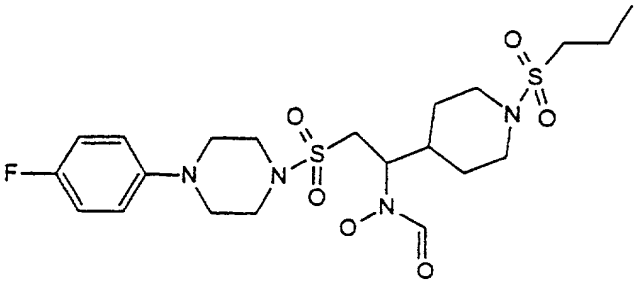

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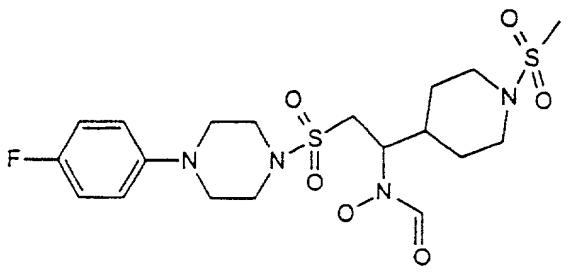
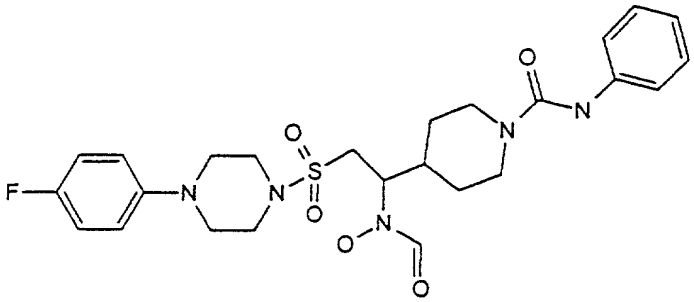


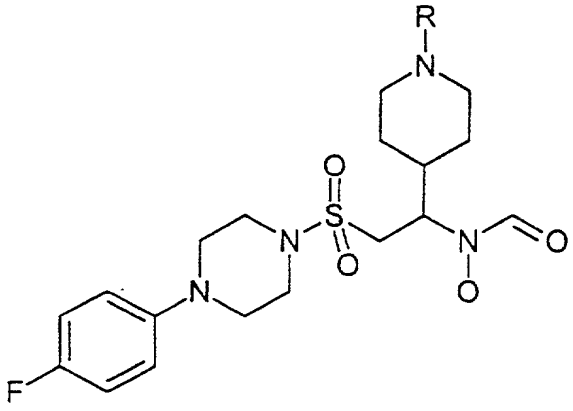
mpt 182

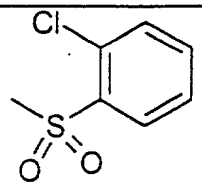
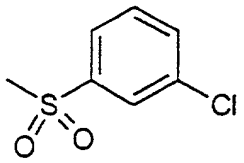
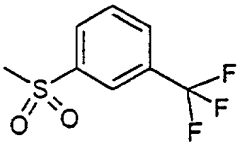
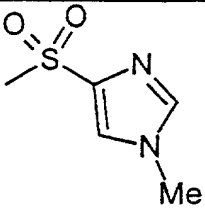
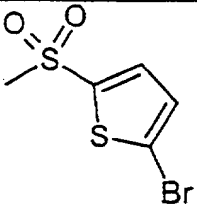
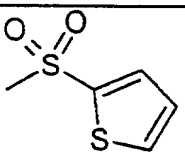
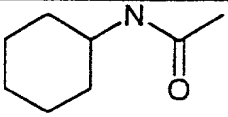


mpt 121

Example 4

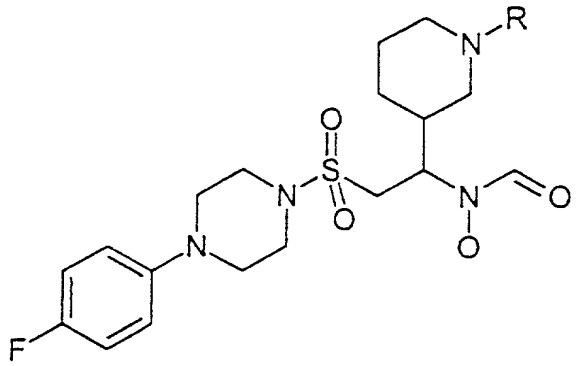
Using procedures analogous to those outlined in Example 1 there were prepared:

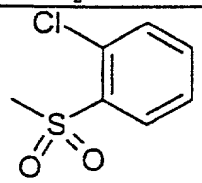
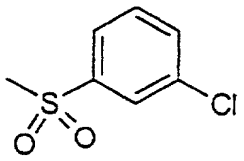
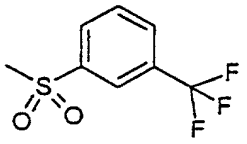
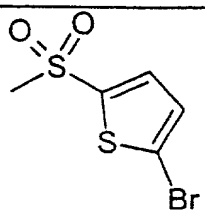
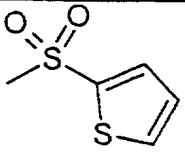


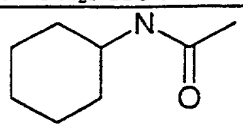
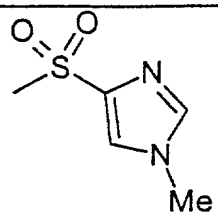
R	MPt °C	M+H
		589
		589
		623
		559
		641
		561
$CF_3CH_2SO_2$-		561
iso-$PrSO_2$-	170-172	
$PhCH_2NHCO$-	130	
	132	
$PhCH_2CH_2NHCO$-	124	
iso-PrNHCO-	155-158	

Example 5

Using procedures analogous to those outlined in Example 1 and using the starting material 1-(t-butoxycarbonyl)-3-formylpiperidine [CAS number 118156-93-7] there were prepared:



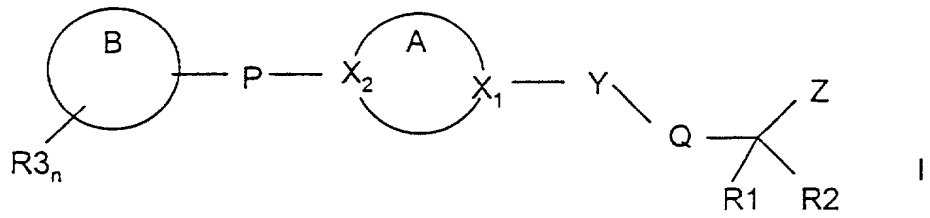
R	MPt °C	M+H
PhCO-		519
n-$PrSO_2$-		521
$MeSO_2$-		493
PhNHCO-		534
$PhSO_2$-		555
		589
		589
	108	
	105	
		561
$CF_3CH_2SO_2$-	87-90	

iso-$PrSO_2$-		521
$PhCH_2NHCO$-	95-100	
	110	
$PhCH_2CH_2NHCO$-	90	
iso-PrNHCO-	95-97	
		559

CLAIMS:

What we claim is:-

1. A compound of the formula I



I

wherein ring B is a monocyclic or bicyclic alkyl, aryl, aralkyl, heteroaryl or heteroaralkyl ring comprising up to 12 ring atoms and containing one or more heteroatoms independently chosen from N, O, and S; alternatively ring B may be biphenyl; ring B may optionally be linked to ring A by a C1-4 alkyl or a C1-4 alkoxy chain linking the 2-position of ring B with a carbon atom alpha to X2;

each R3 is independently selected from hydrogen, halogen, NO2, COOR wherein R is hydrogen or C1-6alkyl, CN, CF3, C1-6 alkyl, -S-C1-6 alkyl, -SO-C1-6 alkyl, -SO2-C1-6 alkyl ,C1-6 alkoxy and up to C10 aryloxy, n is 1,2 or 3;

P is -(CH_2)n- wherein n = 0, 1, 2, or P is an alkene or alkyne chain of up to six carbon atoms; where X2 is C, P may be -Het-, -(CH[R6])n-Het-, -Het-(CH[R6]n-or -Het-(CH[R6])n-Het-, wherein Het is selected from - CO-, -S-, SO-, -SO2-, -NR6- , or -O- wherein n is 1 or 2, or P may be selected from -CO-N(R6)-, -N(R6)-CO-, -SO2-N(R6)- and -N(R6)-SO2-, and R6 is hydrogen, C1-6 alkyl, up to C10 aralkyl or up to C9 heteroalkyl;

Ring A is a 5-7 membered aliphatic ring and may optionally be mono- or di-substituted by optionally substituted C1-6 alkyl or C1-6 alkoxy, each substituent being independently selected from halogen, C1-6 alkyl or an oxo group;

X1 and X2 are independently selected from N and C, where a ring substituent on ring A is an oxo group this is preferably adjacent a ring nitrogen atom;

Y is selected from -SO2- and -CO-;

Z is -CONHOH , Y is -CO- and Q is selected from -C(R6)(R7)-, -C(R6)(R7)-CH2-, -N(R6)-, and -N(R6)-CH2- wherein R6 is as defined above, and solely in relation to Q as here defined, R6 may also represent up to C10 aryl and up to C9 heteroaryl, and R7 is H, C1-6

alkyl, or together with R6 forms a carbocyclic or heterocyclic spiro 5, 6 or 7 membered ring, the latter containing at least one heteroatom selected from N, O, and S;

Z is -CONHOH, Y is -SO2- and Q is selected from -C(R6)(R7)-, and —C(R6)(R7)-CH2-;

or Z is -N(OH)CHO and Q is selected from -CH(R6)-,-CH(R6)-CH2-, and -N(R6)-CH2-;

R1 is H, or C1-6 alkyl;

Z is selected from -COOH, -CONHOH, -N(OH)CHO and N(OH)COR wherein R is C1-6alkyl, up to C10 aryl and up to C9 aralkyl

and R2 is a heterocyclylalkyl ring having 5-7 ring atoms and comprising one or two ring heteroatoms independently selected from oxygen, nitrogen and sulphur, the ring being optionally substituted by (i) Y-R9 wherein R9 is C1-6 alkyl, up to C10 aryl, up to C12 aralkyl or up to C12 heteroaryl(hetero)alkyl, or (ii) Y-T-R9 wherein Y and R9 are as previously defined and T is oxygen or N-R8 wherein R8 is hydrogen or C1-6 alkyl, the heteroatom(s) being independently selected from oxygen, nitrogen and sulphur; R9 and R8 independently being optionally substituted by one or two groups selected from halogen, NO2, CN, CF3, C1-6 alkyl, -S-C1-6 alkyl, -SO-C1-6 alkyl, -SO2-C1-6 alkyl and C1-6 alkoxy;

or a pharmaceutically-acceptable salt or in vivo hydrolysable precursor thereof.

2. A compound as claimed in claim 1 and wherein:

ring A is a 5-6 membered aliphatic ring and is optionally mono- or di-substituted by optionally substituted C1-6 alkyl or C1-6 alkoxy, each substituent being independently selected from halogen, C1-6 alkyl or an oxo group;

R3 is hydrogen, halogen, NO2, CF3, C1-4 alkyl, and C1-4 alkoxy;

n is 1 or 2;

ring B is monocyclic or bicyclic cycloalkyl, aryl, aralkyl or heteroaryl having up to 10 ring atoms;

P is -(CH2)n- wherein n is 0 or 1, or P is -NH-CO-;

one or both of X2 and X1 = N;

Y is -SO2- or -CO-;

Q is -CH(R6)-, -CH(R6)-CH2-, -N(R6)-, and -N(R6)-CH2- wherein R6 is hydrogen or C1-6 alkyl; when Q = -N(R6)-, or -N(R6)-CH2- then Y may also be -CS-, also Q may be linked to R1 or R2 to form a 5-7 alkyl or heteroalkyl ring;

R1 = hydrogen, or C1-4 alkyl.

Z = -CONHOH- or -N(OH)CHO

and R2 is a heterocyclylalkyl ring having 5-7 ring atoms and comprising one or two ring heteroatoms independently selected from oxygen, nitrogen and sulphur, the ring being optionally substituted by (i) Y-R9 wherein R9 is C1-6 alkyl, up to C10 aryl, up to C12 aralkyl or up to C12 heteroaryl(hetero)alkyl, or (ii) Y-T-R9 wherein Y and R9 are as stated in claim 1 and T is oxygen or N-R8 wherein R8 is hydrogen or C1-6alkyl, the heteroatom(s) being independently selected from oxygen, nitrogen and sulphur; R9 and R8 independently being optionally substituted by one or two groups selected from halogen, NO2, CN, CF3, C1-6 alkyl, -S-C1-6 alkyl, -SO-C1-6 alkyl, -SO2-C1-6 alkyl and C1-6 alkoxy;

or a pharmaceutically-acceptable salt or in vivo hydrolysable precursor thereof.

3. A compound as claimed in claim 1 and wherein:

R3 is hydrogen, chlorine, fluorine, NO2, CF3, methyl, ethyl, methoxy, ethoxy;

ring B is phenyl, biphenyl, napthyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl;

P is a direct bond;

both X2 and X1 are N;

Y is -SO2-;

Q is -CH2-;

R2 is a heterocyclylalkyl ring having 5-7 ring atoms and comprising one or two ring heteroatoms independently selected from oxygen, nitrogen and sulphur, the ring being optionally substituted by (i) Y-R9 wherein Y is as stated in claim 1 and R9 is C1-6 alkyl or alkylamino, up to C10 aryl or arylamino, up to C12 aralkyl or aralkylamino, up to C12 heteroaryl(hetero)alkyl, R9 independently being optionally substituted by one or two groups selected from halogen, NO2, CN, CF3, C1-6 alkyl, -S-C1-6 alkyl, -SO-C1-6 alkyl, -SO2-C1-6 alkyl and C1-6 alkoxy;

R1 is hydrogen;

Z is -N(OH)CHO;

or a pharmaceutically-acceptable salt or in vivo hydrolysable precursor thereof.

4. A compound as claimed in claim 1 and wherein:

R3 is methoxy, fluorine or 4-fluoro;

ring A is unsubsituted;

ring B is phenyl, pyridyl, or 2-pyridyl;

R2 is optionally substituted 3-piperidinyl, 4-piperidinyl or N-substituted 4-piperidinyl, wherein the substituents are as stated in claim 3;

or a pharmaceutically-acceptable salt or in vivo hydrolysable precursor thereof.

5. A compound as claimed in claim 1 and wherein R2 is 3- or 4-piperidinyl, optionally N-substituted by Y-R9 wherein Y is as stated in claim 1 and R9 is C1-4 alkyl or alkylamino, C6 aryl or arylamino, up to C10 aralkyl or aralkylamino or up to C10 heteroaryl(hetero)alkyl, R9 independently being optionally substituted by one or two groups selected from halogen, CF3, and C1-4 alkyl;

or a pharmaceutically-acceptable salt or in vivo hydrolysable precursor thereof.

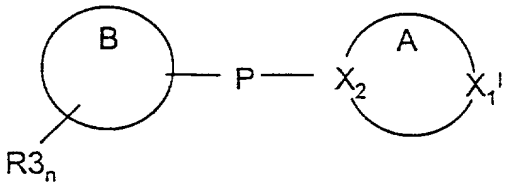
6. A pharmaceutical composition which comprises a compound of the formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt or an in vivo hydrolysable ester and a pharmaceutically acceptable carrier.

7. A compound of the formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof for use in a method of therapeutic treatment of the human or animal body.

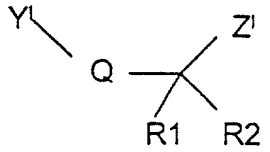
8. A method of treating a metalloproteinase mediated disease condition which comprises administering to a warm-blooded animal a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof.

9. A process for preparing a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof which process comprises

a) reacting a compound of the formula (II) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof with a compound of the formula (III)



II



III

wherein X_1^I represents X or a precursor of X (whether by modification or displacement) or an activated form of X suitable for reaction with Y_1;

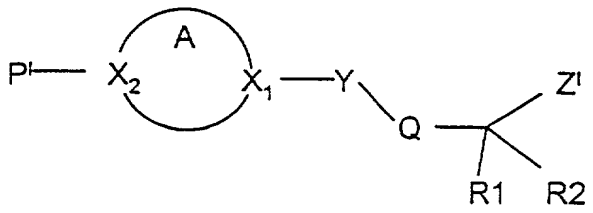
Y_1 represents Y, a precursor of Y, or an activated form of Y suitable for reaction with X_1^I;

by way of non-limiting example, when X is C then X_1 may be derivatised to include a precursor of Y for reaction with a compound of formula III wherein Y^I is a precursor of Y;

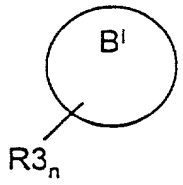
Z^I represents a protected form of Z, a precursor of Z (whether by modification or displacement of Z^I) or an activated form of Z;

or

b) reacting a compound of the formual (IV)) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof with a compound of the formula (V).



IV



V

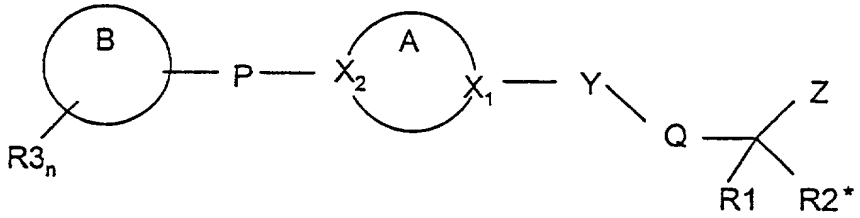
wherein B^I represents a suitable ring function or substituent group for reaction with P^i;

Z^I is as hereinbefore defined; and

P^i represents a suitably activated form of the linker P for reaction with A^I;

or

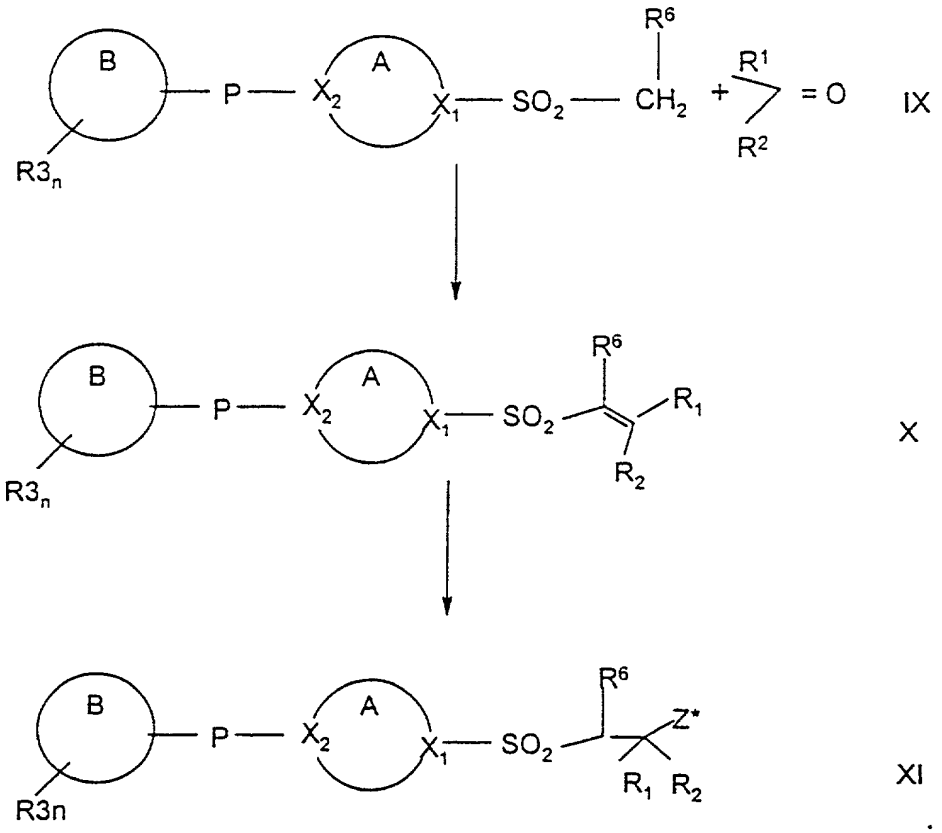
c) reacting a compound of the general formula (VIII)



wherein R2* is a precursor for R2 with appropriate reagent(s) in one or more steps to yield R2. The group Z is conveniently protected during such steps. By way of non-limiting example R2* is a piperidine or piperazine ring;

or

(d) reacting a compound of the formula IX with an appropriate compound of the formula R1-CO-R2 to yield an alkene of the formula X, which is then converted to a compound of the formula XI wherein Z* is a hydroxylamine precursor of the group Z, and then converting Z* to the group Z, all as set out below:



10. The use of a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable precursor thereof in the preparation of a medicament for use in a disease condition mediated by one or more metalloproteinase enzymes.

11. The use of a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable precursor thereof in the preparation of a medicament for use in the treatment of arthritis.

12. The use of a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable precursor thereof in the preparation of a medicament for use in the treatment of atherosclerosis.

Docket. No. Z70554-1P US

DECLARATION (37 C.F.R. § 1.63) AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

the specification of which

- ☐ is attached hereto.
- ☐ was filed on as Application No. and was amended on .
- ☒ was filed on 31.05.2000 as PCT International Application No. PCT/GB00/02085 and was amended under PCT Article 19 on , if applicable.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with 37 C.F.R. § 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119, of any United States provisional applications or foreign application(s) for patent or inventor's certificate or of any PCT International Application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT International Application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application on which priority is claimed:

Application Serial No.	Country	Filing Date (Day/Month/Year)	Priority Claimed (Yes/No)
99401350.6	European Patent Convention	04 June 1999	Yes

Docket. No. _____

I hereby claim the benefit under Title 35, United States Code, Section 120, of any United States application(s) or PCT International Application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56, which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (Patented, Pending, Abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Docket. No. _____

I hereby appoint William P. Atkins, Reg. No. 38,821; Jack S. Barufka, Reg. No. 37,087; W. Patrick Bengtsson, Reg. No. 32,456; Donald J. Bird, Reg. No. 25,323; Kendrew H. Colton, Reg. No. 30,368; Michael R. Dzwonczyk, Reg. No. 36,787; Lynn E. Eccleston, Reg. No. 35,861; G. Paul Edgell, Reg. No. 24,238; Jay M. Finkelstein, Reg. No. 21,082; Stephen C. Glazier, Reg. No. 31,361; Peter W. Gowdey, Reg. No. 25,872; Adam R. Hess, Reg. No. 41,835; David A. Jakopin, Reg. No. 32,995; Kevin E. Joyce, Reg. No. 20,508; Timothy J. Klima, Reg. No. 34,852; G. Lloyd Knight, Reg. No. 17,698; Paul N. Kokulis, Reg. No. 16,773; Dale S. Lazar, Reg. No. 28,872; Raymond F. Lippitt, Reg. No. 17519; Carl G. Love, Reg. No. 18,781; Paul F. McQuade, Reg. No. 31,542; Ruth N. Morduch, Reg. No. 31,044; Mark G. Paulson, Reg. No. 30,793; Glenn J. Perry, Reg. No. 28,458; Michael A. Sanzo, Reg. No. 36,912; Paul L. Sharer, Reg. No. 36,004; George M. Sirilla, Reg. No. 18,221; Paul E. White, Jr., Reg. No. 32,011; Roger R. Wise, Reg. No. 31,204; Richard H. Zaitlen, Reg. No. 27,248, all registered to practice before the Patent and Trademark Office, as my attorneys with full power of substitution and revocation to prosecute this application and all divisions and continuations thereof and to transact all business in the Patent and Trademark Office connected therewith and request that all correspondence and telephone communications be directed to the following person(s) at the mailing address and telephone number hereafter given:

Name:	Donald J. Bird
Registration No.:	25,323
Address:	Pillsbury Madison & Sutro LLP 1600 Tysons Boulevard McLean, VA 22102
Telephone No.:	703-905-2000

Docket. No. _____

Inventor's Signature Howard Tucker Date 20/11/2001

Full name of sole or first inventor: TUCKER, Howard
Residence Address: Macclesfield, Cheshire, United Kingdom GBX
Citizenship: Great Britain
Post Office Address:

Alderley Park
Macclesfield Cheshire SK10 4TG
United Kingdom

Inventor's Signature _____ Date _____

Full name of second joint inventor:
Residence Address:
Citizenship:
Post Office Address:

Inventor's Signature _____ Date _____

Full name of third joint inventor:
Residence Address:
Citizenship:
Post Office Address: